Exhibit 2

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

November 07, 1996

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: *07/131,442*
FILING DATE: *December 11, 1987*
TITLE OF INVENTION:
PHARMACEUTICAL COMPOSITIONS
INVENTOR(S):
LONG, DAVID R.

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

P. SWAIN
Certifying Officer

[redacted]

APPLICATION HAS BECOME ABANDONED. THIS NOTICE MAILED:

SERIAL NUMBER (Series of 1987)	PATENT DATE	PATENT NUMBER
131442		

SERIAL NUMBER	FILING DATE	CLASS	SUBCLASS	GROUP ART UNIT	EXAMINER
07/131,442	12/11/87	514	465	1205	Nichols

APPLICANTS: DAVID R. LONG, ROYSTON, ENGLAND.

CONTINUING DATA********

VERIFIED

FOREIGN/PCT APPLICATIONS********

VERIFIED UNITED KINGDOM 8629751 12/12/86

Foreign priority claimed 35 USC 119 conditions met	Verified and Acknowledged	Examiner's Initials	AS FILED	STATE OR COUNTRY	SHEETS DRWGS.	TOTAL CLAIMS	INDEP. CLAIMS	FILING FEE RECEIVED	ATTORNEY'S DOCKET NO.
yes / no	yes / no		→	GB2	0	14	2	$ 340.00	PEFJIM5597

ADDRESS:
BACON & THOMAS
625 SLATERS LANE - 4TH FLOOR
ALEXANDRIA, VA 22314

TITLE: PHARMACEUTICAL COMPOSITIONS

U.S. DEPT. of COMM.-Pat. & TM Office — PTO-436L (rev. 10-78)

PARTS OF APPLICATION FILED SEPARATELY

NOTICE OF ALLOWANCE MAILED	PREPARED FOR ISSUE		CLAIMS ALLOWED	
	Assistant Examiner	Docket Clerk	Total Claims	Print Claim
ISSUE FEE			DRAWING	
Amount Due / Date Paid		Primary Examiner	Sheets Drwg. / Figs. Drwg. / Print Fig.	
	ISSUE CLASSIFICATION		ISSUE BATCH NUMBER	
	Class / Subclass			

[redacted]

Case Docket No.: REFJIM5557

THE MISSIONER OF PATENTS AND TRADEMARKS
Washington, DC 20231

Sir:

Transmitted herewith for filing is the patent application of:

Inventor: David Richard LONG

For: PHARMACEUTICAL COMPOSITIONS

Enclosed are:

☐ _____ sheet of drawings (☐ Formal ☐ Informal)

☐ An assignment of the invention to _____

☐ A certified copy of a _____ application. Priority is claimed if claim not already of record.

☐ A verified statement to establish small entity status under 37 CFR 1.9 and 37 CFR 1.27.

☐ _____

The filing fee has been calculated as shown below:

ITEM AS FILED		NO. EXTRA	SMALL ENTITY	FULL FEE
Basic Fee			$170	$340
Total Claims	14 -20 =	① 0	x6 =	x12 = 0
Indep. Claims	2 -3 =	② 0	x17 =	x34 = 0
☐ Multiple Dep. Cl. In Proper Form Presented			($55)	($110)
		TOTAL	$	$ 340

① If less than 20 filed, enter "0". ② If less than 3 filed, enter "0".

☐ Please charge my Deposit Account No. 02-0200 in the amount of $_____ to cover the filing fee (and assignment recording fee, if any). A duplicate copy of this sheet is enclosed.

☒ A check in the amount of $ 340 to cover the filing fee (and assignment recording fee, if any) is enclosed.

☒ The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 02-0200. A duplicate copy of this sheet is enclosed.

- ☐ Any additional filing fees required under 37 CFR 1.16.
- ☒ Any additional filing fees required under 37 CFR 1.16, except claim fees under 1.16(b)(c) or (d).
- ☐ Any patent application processing fees under 37 CFR 1.17.

☐ The Commissioner is hereby authorized to charge payment of the following fees during the pendency of this application or credit any overpayment to Deposit Account No. 02-0200. A duplicate copy of this sheet is enclosed.

- ☐ Any patent application processing fees under 37 CFR 1.17.
- ☐ The issue fee set in 37 CFR 1.18 at or before mailing of the Notice of Allowance, pursuant to 37 CFR 1.311(b).
- ☐ Any filing fees under 37 CFR 1.16 for presentation of extra claims.

BACON & THOMAS
625 Slaters Lane - Fourth Floor
Alexandria, Virginia 22314
(703) 683-0500

Date: December 11, 1987

Respectfully submitted,

RICHARD E. FICHTER
Reg. No. 26,382

PATENT APPLICATION SERIAL NO. 131442

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

040 12/17/87 131442 : 101 340.00 CK

PTO-1556
(5/87)

61

340/101

- 1 -

131442

PHARMACEUTICAL COMPOSITIONS

The present invention relates to a pharmaceutical composition containing as active ingredient the histamine H_2 antagonist ranitidine.

Ranitidine, [N-[2-[[[5-(dimethylamino)methyl-2-furanyl]methyl]-thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, and its physiologically acceptable salts are described in British Patent Specification No. 1565966. In that specification there is reference to liquid formulations for oral and parenteral administrations and there is a description of an aqueous based formulation for intravenous use and another of an oral syrup. Both of these formulations contained sufficient hydrochloric acid to achieve a pH of 5.0 and the syrups also contained Sorbitol solution BPC and a flavour as required.

British Patent Application No. GB 2142820A describes aqueous based formulations containing ranitidine and/or one or more of its physiologically acceptable salts thereof having a pH within the range 6.5-7.5. In that specification there is reference to liquid formulations for oral and parenteral administration and there are examples of aqueous formulations for intravenous and oral use. These formulations contain ranitidine hyrochloride and are buffered to a pH of approximately 7 and for intravenous administration the formulations also contain phenol or sodium chloride. For oral administration the formulation also contains hydroxypropylmethyl cellulose as a viscosity enhancing agent, a preservative (parabens), a sweetening agent and a flavour. These compositions have a significantly greater shelf-life over those in British Patent No. 1565966.

We have now surprisingly found that the stability of ranitidine in aqueous based formulations and more particularly aqueous based formulations for oral administration may be substantially enhanced by the addition of ethanol to the formulation.

Thus the present invention provides a pharmaceutical composition which is an aqueous formulation of ranitidine and/or one or more physiologically acceptable salts thereof also containing ethanol. The aqueous formulation is prepared using ingredients of a purity such that it is suitable for administration to patients and will in general

contain at least one conventional pharmaceutical excipient in addition to the ethanol and ranitidine and/or physiologically acceptable salts thereof.

The amount of ethanol present in the formulation is such that the resulting formulation has the enhanced stability. Preferably the amount of ethanol in the composition on a weight/volume basis of the complete formulation, is within the range 2.5% to 10%, and more particularly is between 5 to 10% w/v, more especially 7-8% w/v.

Preferred compositions according to the invention are those in which the pH of the aqueous formulation is within the range 6.5 to 7.5, particularly 6.8 to 7.4 and more especially 7 to 7.3. The required pH of the formulation is preferably obtained by the use of suitable buffer salts for example, potassium dihydrogen orthophosphate and disodium hydrogen orthophosphate or citric acid and disodium hydrogen orthophosphate.

A preferred embodiment of the invention is an aqueous formulation for oral administration. Such a formulation may comprise ranitidine and/or one or more of its physiologically acceptable salts dissolved in water, ethanol, a preservative and a viscosity enhancing agent. Preferably the required pH of the formulation is obtained by the use of appropriate buffer salts. Optionally the composition may also contain other conventional excipients such as a sweetener, a flavour and/or flavouring aids.

Examples of suitable preservatives include one or more alkyl hydroxybenzoates such as methyl, ethyl, propyl and/or butyl hydroxybenzoates.

Examples of suitable viscosity enhancing agents include Xanthan gum, sorbitol glycerol, sucrose or a cellulose derivative such as carboxymethylcellulose or a salt thereof of a C_{1-4} alkyl and/or a hydroxy-C_{2-4}alkyl ether of cellulose such as methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose and hydroxypropylmethylcellulose.

Examples of suitable sweeteners include saccharin sodium, sodium cyclamate, sorbitol and sucrose.

Examples of suitable flavouring agents include 'mint' flavours such as peppermint flavouring agents.

The concentration of ranitidine in the oral formulation, expressed as free base, is conveniently within the range 20-400mg per 10ml, for example 20-200 mg per 10ml, more particularly 150mg per 10ml dose.

The amount of ethanol in the formulation for oral administration, expressed as a percentage of the complete formulation on a weight/volume basis, is preferably within the range 2.5 to 10%, and more particularly between 5 to 10%, more especially 7-8%.

The amount of viscosity enhancing agent in the formulation will preferably be sufficient to give a solution with a viscosity in the range of 10 to 100 centipoises.

The aqueous formulations for oral administration are conveniently prepared by mixing an aqueous solution of ranitidine and/or one or more of its physiologically acceptable salts together with ethanol and the excipients, with aqueous solution or dispersion of the viscosity ennancing agent.

The aqueous formulations according to the invention are preferably prepared using ranitidine in the form of its hydrochloride salt.

An illustrative example of a formulation according to the invention is as follows. In this example the relative proportions of ranitidine hydrochloride and the buffer salts are such that the formulation has a pH of approximately 7.

Ranitidine oral liquid formulation (150mg/10ml) expressed as free base

	% w/v
Ranitidine hydrochloride	1.68
Ethanol	7.5
Potassium dihydrogen orthophosphate	0.095
Disodium hydrogen orthophosphate anhydrous	0.350
Hydroxypropylmethylcellulose	qs
Preservative	qs
Sweetening agents	qs
Flavour	qs
Purified water BP to	100ml

CLAIMS

1. A pharmaceutical composition which is an aqueous formulation of ranitidine and/or one or more physiologically acceptable salts thereof, said formulation also containing ethanol.

2. A pharmaceutical composition according to claim 1 containing 2.5% to 10% weight/volume ethanol based on the complete formulation.

3. A pharmaceutical composition according to claim 1 containing 7% to 8% weight/volume ethanol based on the complete formulation.

4. A pharmaceutical composition according to claim 1 having a pH in the range 6.5 to 7.5.

5. A pharmaceutical composition according to claim 1 having a pH in the range 6.8 to 7.4.

6. A pharmaceutical composition according to claim 1 having a pH in the range 7.0 to 7.3.

7. A pharmaceutical composition according to claim 1 wherein said pH is obtained by the use of buffer salts.

8. A pharmaceutical composition as claimed in claim 1 suitable for oral administration.

9. A pharmaceutical composition as claimed in claim 8 containing 20-400 mg ranitidine per 10 ml dose expressed as free base.

10. A pharmaceutical composition according to claim 8 containing 20-200 mg ranitidine per 10 ml dose expressed as free base.

11. A pharmaceutical composition according to claim 8 containing 150 mg ranitidine per 10 ml dose expressed as free base.

12. A pharmaceutical composition according to claim 1 prepared using ranitidine in the form of the hydrochloride salt.

13. A pharmaceutical composition which is an aqueous formulation of ranitidine suitable for oral administration containing 150 mg ranitidine per 10 ml dose expressed as free base, said formulation having a pH in the range 7.0 to 7.3 and also containing 7% to 8% weight/volume ethanol based on the complete formulation.

14. A pharmaceutical composition according to claim 13 wherein said pH is obtained by the use of buffer salts.

ABSTRACT

The stability of aqueous formulations of ranitidine or a physiologically acceptable salt thereof is enhanced by the addition of ethanol.

Attorney/Docket No. _____

DECLARATION FOR PATENT APPLICATION
AND APPOINTMENT OF ATTORNEY

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name; I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention (Design, if applicable) entitled

Pharmaceutical Compositions

the specification of which (check one): [ ] is attached hereto; [ ] was filed on _____ as Application Serial No. _____ and was amended on (or amended through) _____ (if applicable); was filed as International Application (PCT) No. _____ and amended on _____ (if applicable). I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a). I hereby claim foreign priority benefits under Title 35, United States Code §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Claimed	
86 29781	United Kingdom	12th December, 1986	[X]	[ ]
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
			[ ]	[ ]
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
			[ ]	[ ]
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
			[ ]	[ ]
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Appln. SN)	(Filing Date)	(Status - Patented, Pending or Abandoned)
(Appln. SN)	(Filing Date)	(Status - Patented, Pending or Abandoned)

I HEREBY DECLARE THAT ALL STATEMENTS MADE HEREIN OF MY OWN KNOWLEDGE ARE TRUE AND THAT ALL STATEMENTS ... ON INFORMATION AND BELIEF ARE BELIEVED TO BE TRUE; AND FURTHER THAT THESE STATEMENTS WERE MADE WITH THE ...LEDGE THAT WILLFUL FALSE STATEMENTS AND THE LIKE SO MADE ARE PUNISHABLE BY FINE OR IMPRISONMENT, OR BOTH, UNDER SECTION 1001 OF TITLE 18 OF THE UNITED STATES CODE AND THAT SUCH WILLFUL FALSE STATEMENTS MAY JEOPARDIZE THE VALIDITY OF THE APPLICATION OR ANY PATENT ISSUED THEREON.

7

DECLARATION FOR PATENT APPLICATION
AND APPOINTMENT OF ATTORNEY
Page 2

Attorney/Docket No. _____

POWER OF ATTORNEY: I (We) hereby appoint as my (our) attorneys, with full powers of substitution and revocation, to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: J. Ernest Kenney, Reg. No. 19,179; Eugene Mar, Reg. No. 25,893; Richard E. Fichter, Reg. No. 26,382; Charles R. Wolfe, Jr., Reg. No. 28,680; Bruce H. Troxell, Reg. No. 26,592; Thomas J. Moore, Reg. No. 28,974;

Send correspondence to: BACON & THOMAS
625 Slaters Lane - 4th Floor
Alexandria, VA 22314

Telephone Calls to:
(703) 683-0500

Full Name of First or Sole Inventor	Citizenship
Dr. David Richard Long,	British
RESIDENCE Address - Street	Post Office Address - Street
41, Echo Hill,	41, Echo Hill,
City	City
Royston,	Royston
State or Country Zip	State or Country Zip
Hertfordshire,	ENGLAND.
Date	Signature
07 Dec. 1987	DR Long

Full Name of Joint Inventor	Citizenship
RESIDENCE Address - Street	Post Office Address - Street
City	City
State or Country Zip	State or Country Zip
Date	Signature

Full Name of Joint Inventor	Citizenship
RESIDENCE Address - Street	Post Office Address - Street
City	City
State or Country Zip	State or Country Zip
Date	Signature

Full Name of Joint Inventor	Citizenship
RESIDENCE Address - Street	Post Office Address - Street
City	City
State or Country Zip	State or Country Zip
Date	Signature

(See following page(s) for additional joint inventors)

/Continued.....

131442

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

David Richard LONG

Filed: Herewith

For: PHARMACEUTICAL COMPOSITIONS

PRELIMINARY AMENDMENT

Honorable Commissioner of Patents and
Trademarks
Washington, D.C. 20231

SIR:

Prior to an examination on the merits, please amend the accompanying application as follows:

In the Specification:

Page 2, line 28, please insert a comma after "sorbitol".

Page 2, line 29, please delete delete "of" and insert therefor --or--.

REMARKS

The specification of the above-identified new application has been amended to correct obvious typographical errors and is not meant to change the meaning of the invention but corrects the errors in order to more clearly define the present invention.

Respectfully submitted,

Richard E. Fichter
Reg. No. 26,382

BACON & THOMAS
625 Slaters Lane
Fourth Floor
Alexandria, VA 22314

December 11, 1987

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4/4/88

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

David Richard LONG

12X

Serial No. 131,442

Group Art Unit: 123

Filed: December 11, 1987

J. FRIEDMAN

For: PHARMACEUTICAL COMPOSITIONS

COMPLETION OF CLAIM FOR PRIORITY

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

Attached hereto is a certified copy of UK Application No. GB 8629781, dated December 12, 1986, to complete the claim for priority made in the Declaration of the above-identified application.

Respectfully submitted,

Richard E. Fichter

Richard E. Fichter
Reg. No. 26,382

BACON & THOMAS
625 Slaters Lane, Fourth Floor
Alexandria, VA 22314

(703) 683-0500

Date: March 11, 1988
/bjr

12

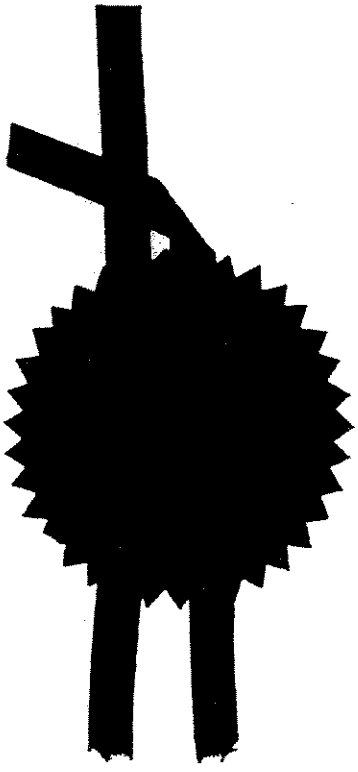
THE PATENT OFFICE
STATE HOUSE
66–71 HIGH HOLBORN
LONDON WC1R 4TP

cut by
Certification Branch

I, the undersigned, being an officer duly authorised in accordance with Section 62(3) of the Patents and Designs Act 1907, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents, has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or the inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.



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PATENTS ACT 1977

PATENTS FORM No. 1/77 (Revised 1982)
(Rules 16, 19)

12 DEC 1986

The Comptroller
The Patent Office

1986
29781

REQUEST FOR GRANT OF A PATENT

8629781

THE GRANT OF A PATENT IS REQUESTED BY THE UNDERSIGNED ON THE BASIS OF THE PRESENT APPLICATION

I Applicant's or Agent's Reference *(Please insert if available)* HA107

II Title of Invention PHARMACEUTICAL COMPOSITIONS

III Applicant or Applicants *(See note 2)*

Name (First or only applicant) Glaxo Group Limited

Country United Kingdom State ADP Code No.

Address Clarges House, 6-12 Clarges Street, London W1Y 8DH, England.

Name (of second applicant, if more than one)

Country State

Address

IV Inventor (see note 3)

(b) A statement on Patents Form No 7/77 will be furnished

V Name of Agent (if any) *(See note 4)* ELKINGTON AND FIFE ADP CODE NO

VI Address for Service (See note 5) High Holborn House
52/54 High Holborn
London WC1V 6SH

VII Declaration of Priority (See note 6)

Country	Filing date	File number
	-	-

VIII The Application claims an earlier date under Section 8(3), 12(6), 15(4), or 37(4) (See note 7

Earlier application or patent number and filing date

13 Jan
17

IX Check List *(To be filled in by applicant or agent)*

A The application contains the following number of sheet(s):

1 Request ... Sheet(s) 1
2 Description ... Sheet(s) 4
3 Claim(s) ... Sheet(s)
4 Drawing(s) ... Sheet(s)
5 Abstract ... Sheet(s)

B The application is filed with the following:

1 Priority document
2 Translation of priority document
3 Request for Search
4 Statement of Inventorship and Right to Grant

X It is suggested that Figure No ... of the drawings (if any) should accompany the abstract when published.

XI Signature *(See note 8)*

ELKINGTON AND FIFE (GAB/LR)

NOTES

1 This form, when completed, should be brought or sent to the Patent Office together with the prescribed fee and two copies of the description of the invention, and of any drawings.

2 Enter the name and address of each applicant. Names of individuals should be indicated in full and the surname or family name should be underlined. The names of all partners in a firm must be given in full. Bodies corporate should be designated by their corporate name and the country of incorporation and, where appropriate, the state of incorporation within that country should be entered where provided. Full corporate details, eg "a corporation organised and existing under the laws of the State of Delaware, United States of America," trading styles, eg "trading as xyz company", nationality, and former names, eg "formerly (known as) ABC Ltd." are not required and should not be given. Also enter applicant(s) ADP Code No (if known).

3 Where the applicant or applicants is/are the sole inventor or the joint inventors, the declaration (a) to that effect at IV should be completed, and the alternative statement (b) deleted. If, however, this is not the case the declaration (a) should be struck out and a statement will then be required to be filed upon Patent Form No 7/77.

4 If the applicant has appointed an agent to act on his behalf, the agent's name and the address of his place of business should be indicated in the spaces available at V and VI. Also insert agent's ADP Code No. (if known) in the box provided.

5 An address for service in the United Kingdom to which all documents may be sent must be stated at VI. It is recommended that a telephone number be provided if an agent is not appointed.

6 The declaration of priority at VII should state the date of the previous filing and the country in which it was made and indicate the file number, if available.

7 When an application is made by virtue of section 8(3), 12(6), 15(4) the appropriate section should be identified at VIII and the number of the earlier application or any patent granted thereon identified.

8 Attention is directed to rules 90 and 106 of the Patent Rules 1982.

9 Attention of applicants is drawn to the desirability of avoiding publication of inventions relating to any article, material or device intended or adapted for use in war (Official Secrets Acts, 1911 and 1920). In addition after an application for a patent has been filed at the Patent Office the comptroller will consider whether publication or communication of the invention should be prohibited or restricted under section 22 of the Act and will inform the applicant if such prohibition is necessary.

10 Applicants resident in the United Kingdom are also reminded that, under the provisions of section 23 applications may not be filed abroad without written permission or unless an application has been filed not less than six weeks previously in the United Kingdom for a patent for the same invention and no direction prohibiting publication or communication has been given or any such direction has been received.

PHARMACEUTICAL COMPOSITIONS

The present invention relates to a pharmaceutical composition containing as active ingredient the histamine H_2 antagonist ranitidine.

Ranitidine, [N-[2-[[[5-(dimethylamino)methyl-2-furanyl]methyl]-thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, and its physiologically acceptable salts are described in British Patent Specification No. 1565966. In that specification there is reference to liquid formulations for oral and parenteral administrations and there is a description of an aqueous based formulation for intravenous use and another of an oral syrup. Both of these formulations contained sufficient hydrochloric acid to achieve a pH of 5.0 and the syrups also contained Sorbitol solution BPC and a flavour as required.

British Patent Application No. GB 2142820A describes aqueous based formulations containing ranitidine and/or one or more of its physiologically acceptable salts thereof having a pH within the range 6.5-7.5. In that specification there is reference to liquid formulations for oral and parenteral administration and there are examples of aqueous formulations for intravenous and oral use. These formulations contain ranitidine hyrochloride and are buffered to a pH of approximately 7 and for intravenous administration the formulations also contain phenol or sodium chloride. For oral administration the formulation also contains hydroxypropylmethyl cellulose as a viscosity enhancing agent, a preservative (parabens), a sweetening agent and a flavour. These compositions have a significantly greater shelf-life over those in British Patent No. 1565966.

/5 over

We have now surprisingly found that the stability of ranitidine in aqueous based formulations and more particularly aqueous based formulations for oral administration may be substantially enhanced by the addition of ethanol to the formulation.

Thus the present invention provides a pharmaceutical composition which is an aqueous formulation of ranitidine and/or one or more physiologically acceptable salts thereof also containing ethanol. The aqueous formulation is prepared using ingredients of a purity such that it is suitable for administration to patients and will in general contain at least one conventional pharmaceutical excipient in addition to the ethanol and ranitidine and/or physiologically acceptable salts thereof.

The amount of ethanol present in the formulation is such that the resulting formulation has the enhanced stability. Preferably the amount of ethanol in the composition on a weight/volume basis of the complete formulation, is within the range 2.5% to 10%, and more particularly is between 5 to 10% w/v, more especially 7-8% w/v.

Preferred compositions according to the invention are those in which the pH of the aqueous formulation is within the range 6.5 to 7.5, particularly 6.8 to 7.4 and more especially 7 to 7.3. The required pH of the formulation is preferably obtained by the use of suitable buffer salts for example, potassium dihydrogen orthophosphate and disodium hydrogen orthophosphate or citric acid and disodium hydrogen orthophosphate.

A preferred embodiment of the invention is an aqueous formulation for oral administration. Such a formulation may comprise ranitidine and/or one or more of its physiologically acceptable salts dissolved in water, ethanol, a preservative and a viscosity enhancing agent. Preferably the required pH of the formulation is obtained by the use of appropriate buffer salts. Optionally the composition may

also contain other conventional excipients such as a sweetener, a flavour and/or flavouring aids.

Examples of suitable preservatives include one or more alkyl hydroxybenzoates such as methyl, ethyl, propyl and/or butyl hydroxybenzoates.

Examples of suitable viscosity enhancing agents include Xanthan gum, sorbitol glycerol, sucrose or a cellulose derivative such as carboxymethylcellulose or a salt thereof of a C_{1-4} alkyl and/or a hydroxy-C_{2-4}alkyl ether of cellulose such as methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose and hydroxypropylmethylcellulose.

Examples of suitable sweeteners include saccharin sodium, sodium cyclamate, sorbitol and sucrose.

Examples of suitable flavouring agents include 'mint' flavours such as peppermint flavouring agents.

The concentration of ranitidine in the oral formulation, expressed as free base, is conveniently within the range 20-400mg per 10ml, for example 20-200 mg per 10ml, more particularly 150mg per 10ml dose.

The amount of ethanol in the formulation for oral administration, expressed as a percentage of the complete formulation on a weight/volume basis, is preferably within the range 2.5 to 10%, and more particularly between 5 to 10%, more especially 7-8%.

The amount of viscosity enhancing agent in the formulation will preferably be sufficient to give a solution with a viscosity in the range of 10 to 100 centipoises.

The aqueous formulations for oral administration are

conveniently prepared by mixing an aqueous solution of ranitidine and/or one or more of its physiologically acceptable salts together with ethanol and the excipients, with aqueous solution or dispersion of the viscosity enhancing agent.

The aqueous formulations according to the invention are preferably prepared using ranitidine in the form of its hydrochloride salt.

An illustrative example of a formulation according to the invention is as follows. In this example the relative proportions of ranitidine hydrochloride and the buffer salts are such that the formulation has a pH of approximately 7.

Ranitidine oral liquid formulation (150mg/10ml) expressed as free base

	% w/v
Ranitidine hydrochloride	1.68
Ethanol	7.5
Potassium dihydrogen orthophosphate	0.095
Disodium hydrogen orthophosphate anhydrous	0.350
Hydroxypropylmethylcellulose	qs
Preservative	qs
Sweetening agents	qs
Flavour	qs
Purified water BP to	100ml

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

David R. LONG

Serial No. 131,442

Filed: December 11, 1987

For: PHARMACEUTICAL COMPOSITIONS

Group Art Unit: 123

INFORMATION DISCLOSURE STATEMENT

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

Prior to an examination of the merits of the above identified application, the attention of the Examiner is directed to the following information, which may be considered material to the prosecution of the present application. The attached Form PTO-1449 lists the publications, and a copy of each U.S. patent is submitted herewith.

The most relevant publications of which Applicant is aware are British Patent Specification No. 1,565,966 and British Patent Specification No. 2,142,820A. The specifications are discussed at Applicant's specification page 1, lines 4-25. The U.S. equivalents of these publications are U.S. Patent Nos. 4,128,658 and 4,585,790.

U.S. Patent No. 4,585,790 refers to a publication by Padfield et al ("The Chemical Use of Ranitidine," Medicine Publishing Foundation Symposium Series 5, Oxford, Medicine Publishing Foundation 1982 pages 18-22). This publication refers to an aqueous formulation of ranitidine hydrochloride at its natural pH, i.e., about 5.5. This publication is not believed to be as relevant as the publications discussed in Applicant's specification. The Examiner is requested to contact the undersigned if

Serial No. 131,442

a copy of this publication is required.

In view of the above comments and information disclosure, an early action on the merits of this application is now believed to be in order and is most respectfully requested.

Respectfully submitted,

Richard E. Fichter

Richard E. Fichter
Registration No. 26,382

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625 Slaters Lane
Fourth Floor
Alexandria, Virginia 22314
Phone: (703) 683-0500

April 8, 1988

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Sheet 1 of 1

FORM PTO—1449 (Rev. 2-32) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use several sheets if necessary)

ATTY. DOCKET NO.	SERIAL NO.
REF	131
APPLICANT	LONG
FILING DATE	GROUP
12-11-87	125

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
		4128658					
		4585790					

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

Padfield et al, "The Chemical Use of Ranitidine," Medicine Publishing Foundation Symposium Series 5, Oxford, Medicine Publishing Foundation 1982 pages 18-22

EXAMINER | DATE CONSIDERED

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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TO SEPARATE HOLD TOP AND BOTTOM EDGES SNAP APART AND DISCARD CARBON

FORM PTO-892 (REV 3-78) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

NOTICE OF REFERENCES CITED

SERIAL NO	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER
131 442	125	3

APPLICANT(S): Long

U.S. PATENT DOCUMENTS

*		DOCUMENT NO	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	A						
	B						
	C						
	D						
	E						
	F						
	G						
	H						
	I						
	J						
	K						

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS DWG PP SPEC
	L							
	M							
	N							
	O							
	P							
	Q							

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

R Chem. Abst., Vol 97- 61014 G (1982).

S Chem. Abst., Vol. 104- 102280 Z (1986).

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U

EXAMINER	DATE
Friedman, S.J.	4/20/88

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*A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05 (a).)

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/131,442	12/11/87	LONG D	REFJIM5557

BACON & THOMAS
625 SLATERS LANE - 4TH FLOOR
ALEXANDRIA, VA 22314

EXAMINER	
FRIEDMAN, S	
ART UNIT	PAPER NUMBER
125	4

DATE MAILED: 05/05/88

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-14 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-14 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings which are acceptable for examination purposes until such time as allowable subject matter is indicated.
8. ☐ Allowable subject matter having been indicated, formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. These drawings are ☐ acceptable; ☐ not acceptable (see explanation).
10. ☐ The ☐ proposed drawing correction and/or the ☐ proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved. ☐ disapproved (see explanation). However, the Patent and Trademark Office no longer makes drawing changes. It is now applicant's responsibility to ensure that the drawings are corrected. Corrections MUST be effected in accordance with the instructions set forth on the attached letter "INFORMATION ON HOW TO EFFECT DRAWING CHANGES", PTO-1474.
12. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☑ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

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PTOL-326 (Rev. 7-82) EXAMINER'S ACTION

Claim 1-10 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

"Also containing ethanol" (claim 1) is indefinite as to what else is included. All claims should show how the pH is arrived at.

Claim 1-12 rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited in accordance with the entire disclosure. See MPEP 706.03(n) and 706.03(z).

All claims should recite amounts for all imgredients. Claims failing to do such are broader than unwanted.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claim 1-14 rejected under 35 U.S.C. 103 as being unpatentable over Chemical Abstracts, both.

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The art teaches the cojoining of ranitidine and an alcohol; e.g. ethanol. The addition of a non-critical pH limit and non-crital amounts are not seen as patentable limitations to the varioues claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Friedman whose telephone number is (703) 557-9592.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 557-3920.

4-29-88;df

Stanley J. Friedman
Primary Examiner
Group Art Unit 125

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application Serial No.: 131,442

Applicant: LONG

Filing Date: December 11, 1987

Group Art Unit: 125

Examiner: Friedman

For: PHARMACEUTICAL COMPOSITIONS

PETITION FOR EXTENSION OF TIME

Honorable Commissioner of Patents
and Trademarks
Washington, DC 20231

Sir:

Applicant requests that the time for taking action in this case be extended pursuant to 37 CFR 1.136 (a) for:

☐ one month ☒ three months
☐ two months ☐ four months

The fee set in 37 CFR 1.17 for the extension of time is $ 390.00 .

☒ Fee enclosed. Please charge any additional fee required for this extension of time to Deposit Account No. 02-0200 . A duplicate copy of this paper is enclosed.

☐ Charge fee to Deposit Account No. _____ . A duplicate copy of this paper is enclosed.

☐ Applicant is a small entity entitled to pay reduced fees in this application. A verified small entity statement:

☐ has been filed ☐ is enclosed

Also enclosed is a:

☒ Response ☐ Notice of Appeal ☐ Appeal Brief

☐ _____

Respectfully submitted,

Richard E. Fichter
Reg. No. 26,382

BACON & THOMAS
625 Slaters Lane - Fourth Floor
Alexandria, Virginia 22314
(703) 683-0500

Date: November 7, 1988

070 11/09/88 131442
/bjr

1 117 390.00 CK

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application Serial No. 131,442

Applicant: LONG

Group Art Unit: 125

Filing Date: December 11, 1988

Examiner: Friedman

For: PHARMACEUTICAL COMPOSITIONS

AMENDMENT

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

SIR:

This is in response to the Official Action of May 5, 1988 in connection with the above-identified application. The period for response to this Official Action has been extended to expire on November 5, 1988 by the filing herewith of a Petition for three month Extension of Time and payment of the required fee. Please amend the above-identified application as follows:

IN THE CLAIMS

Please amend Claim 1 as follows:

1. (Amended) A pharmaceutical composition which is an aqueous formulation of ranitidine and/or one or more physiologically acceptable salts thereof, said formulation also containing a stabilizing effect amount of ethanol and said composition having a pH in the range of 6.5 to 7.5.

Please cancel Claim 4 without prejudice or disclaimer.

REMARKS

Applicant has amended the claims in order to more particularly define the invention. Claims 1 and 4 have been combined and the amount ethanol present has been functionally defined. Claim 4 has been cancelled from the application. The claims remaining in the application are Claims 1-3 and 5-10. Applicant

most respectfully submits that all the claims now present in the application are in full compliance with 35 USC 112 and are clearly patentable over the references of record.

The rejection of Claims 1-10 under 35 USC 112 second paragraph as being indefinite has been carefully considered. The expression "also containing ethanol" has been modified to specify that the amount of ethanol contained in the composition is a stabilizing amount of ethanol and this amendment is fully supported by applicant's specification, at page 2, lines 4 and 5.

In addition, the pH range from Claim 4 has been included in Claim 1. Applicant most respectfully submits that there is no requirement that the method of obtaining the pH be set forth in the claims. This would be fully appreciated by one of ordinary skill in the art. In fact, the desired pH can be simply achieved by adding an appropriate amount of a physiologically acceptable acid or base to the solution, depending on whether the solution is prepared from ranitidine free base or an acid addition salt thereof. It is not necessary to use buffer salts to obtain the desired pH, although it may often be more convenient to do so. Accordingly, it can be seen that the means for adjusting pH are entirely conventional and therefore, it is most respectfully requested that this aspect of the rejection under 35 USC 112 be withdrawn. As far as Claim 7 is concerned, having inserted the pH range in Claim 1, the amount of buffer salts is thereby predetermined, depending on the specific buffer salts that are used.

The rejections of Claims 1-14 under 35 USC 103 as being unpatentable over Chemical Abstracts has been carefully considered. In the Official Action it is urged that the art teaches the cojoining of ranitidine and an alcohol; e.g., ethanol. The addition of a non-critical pH limitation and non-critical amounts are not seen as patentable limitations to the various claims. This rejection having been carefully considered is most respectfully traversed.

At the outset, applicant specifically traversed the statement in the Official Action that the references relied upon by the Examiner teach the cojoining of ranitidine and an alcohol, e.g., ethanol. Applicant most respectfully submits that the art does not teach the cojoining of ranitidine and an alcohol in a pharmaceutical composition. These references do not lead one

of ordinary skill in the art any way to expect that the stability of ranitidine in an aqueous pharmaceutical compossition could be enhanced by the presence of ethanol and does not suggest the presence of ethanol in such compositions.

The first Chemical Abstract reference (97 61014G) relates to the Glaxo patent for a new polymorphic form of ranitidine hydrochloride (designated form 2) and includes a description of processes for its production. Applicant most respectfully submits that all that one of ordinary skill in the art can infer from this reference is that ranitidine hydrochloride must be reasonably stable in ethanol since ethanol is used as a solvent for recrystallization. However, there is no teaching whatever that the stability of ranitidine or its salts as a solution in water is enhanced by the presence of ethanol and no suggestion that ethanol should be included in pharmaceutical compositions containing ranitidine as presently claimed.

The second Chemical Abstract reference (104 102280z) relates to a paper in a Scandinavian journal indicating the presence of ethanol in a person's diet did not adverserly affect the gastric acid secretion inhibiting properties of ranitidine. Again, there is absolutely no teaching in this reference that would lead one of ordinary skill in the art to expect that ethanol would enhance the stability of ranitidine in aqueous pharmaceutical compositions or would suggest to one of ordinary skill in the art that ethanol should be added to such compositions.

In summary, the prior art relied upon in the rejection is in fact, extremely far removed from the present claimed invention and no way renders it obvious. Accordingly, it is most respectfully requested that this rejection be withdrawn.

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In view of the above comments and amendments to the claims, favorable reconsideration and allowance of all the claims now present in the application are most respectfully requested.

Respectfully submitted,

Richard E. Fichter
Registration No. 26,382

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Date: November 7, 1988